

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 71667

**Title:** Testosterone therapy reduces hepatic steatosis in men with type 2 diabetes and low serum testosterone concentrations

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05264112

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Australia

**Manuscript submission date:** 2021-09-24

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-09-27 13:05

**Reviewer performed review:** 2021-10-01 04:02

**Review time:** 3 Days and 14 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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## **SPECIFIC COMMENTS TO AUTHORS**

In this study, the authors highlighted that treatment of intramuscular testosterone undecanoate could significantly improve NAFLD in men with type 2 diabetes and low testosterone concentrations. In addition, the authors suggested that testosterone therapy increased lean muscle mass and reduced total fat mass. This study was a sub-analysis of a previous randomized controlled trial which had suggested that testosterone therapy could not improve glucose metabolism or visceral adiposity in obese men with moderately controlled T2D and only modest reductions in circulating testosterone levels typical for men with T2D. It was novel that the authors re-analyzed the patients with NAFLD, and using MRI scan for the assessment of hepatic steatosis. It seemed that testosterone therapy was involved with lipid metabolism, not only specifically affecting liver fat, but also body fat. However, visceral adiposity was unchanged. Could the authors explain more in detail about that? Additionally, what might cause the differences in the participants in the index study who did not have MRI scans with lower baseline BMI, visceral adiposity, waist circumference and higher cholesterol levels in Table 2?

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**Title:** Testosterone therapy reduces hepatic steatosis in men with type 2 diabetes and low serum testosterone concentrations

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02459759

**Position:** Associate Editor

**Academic degree:** MD

**Professional title:** Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Australia

**Manuscript submission date:** 2021-09-24

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-09-26 00:35

**Reviewer performed review:** 2021-10-07 12:50

**Review time:** 11 Days and 12 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis, and is more common in subjects with type 2 diabetes mellitus (T2DM). Testosterone therapy has been explored in both animal and human studies with mixed results. Therefore, the aim of this study was to evaluate the effect of testosterone therapy on liver fat fraction and to determine other factors associated with changes in liver fat in a population of men with type 2 diabetes and low testosterone concentrations. Despite these limitations, the results showed that testosterone therapy was associated with a reduction in hepatic steatosis in men with diabetes and low serum testosterone. The paper is sound methodologically, however there are some issues that must be addressed as follows. 1) Due to the small sample size and the differences between participates in our study and those who did not have MRI scans, the results concluded from our study are difficult to generalize. 2) The baseline data did not match between the Testosterone group and the Placebo group, such as Lean mass and HDL. 3) The calculated free testosterone (cFT) should be more specifically illuminated in the Methods section. 4) The formats of the Tables are not standard, and they should be three-line tables with the table heads above the tables. 5) The picture is not well annotated, so what do the red and green lines in Figure 1 and Supplementary Figure 1 represent? In addition, (A) and (B) in Figure 1 and Supplementary Figure 1 should be combined into one figure.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 71667

**Title:** Testosterone therapy reduces hepatic steatosis in men with type 2 diabetes and low serum testosterone concentrations

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02459759

**Position:** Associate Editor

**Academic degree:** MD

**Professional title:** Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Australia

**Manuscript submission date:** 2021-09-24

**Reviewer chosen by:** Li-Li Wang

**Reviewer accepted review:** 2022-01-06 07:04

**Reviewer performed review:** 2022-01-07 02:21

**Review time:** 19 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript was partially revised, but still existed some shortcomings: 1) The formats of the Tables are still not standard, and they should be three-line tables with the headers above the tables and footnotes at the bottom of the tables. 2) The figure titles and legends should be all placed at the bottom of the figures. Additionally, the legend such as "Individual subjects plots of change in liver fat proportion" should be removed from the figure, but the label (A) and (B) should be combined in the figure.